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CLOSURE

SIGNIFICANCE OF DETERMINING THE HYALURONIDASE ACTIVITY  
OF BLOOD SERUM IN GASTRIC CANCER

by A. V. Pavlyushchik

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FOREWORD

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SIGNIFICANCE OF DETERMINING THE HYALURONIDASE ACTIVITY  
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[Following is a translation of an article by A. V. Pavlyushchik in the Russian-language periodical Zdravookhraneniye Belorussii (Public Health in Belorussia), Minsk, Vol. VI, No. 4, April 1960, pages 18-20.]

(A. V. Pavlyushchik is a graduate student in the Department of Surgery of the Belorussian Institute of Post-graduate Training for Physicians (director, Professor A. M. Boldin) and the Department of General Chemistry of the Minsk Medical Institute (director, Docent V. A. Bandarin).)

Hyaluronic acid was first isolated by Meyer and Palmer (1934, 1936) from the vitreous humor of the eye. The white substance obtained contained 5.16% nitrogen, 60.2% reducing matter, 20.5 hexuronic acid and 3.48% ash. It is contained in large amounts in the umbilical cord of man and cattle, and in the synovial fluids. Hyaluronic acid dissolves easily in water, forming colloidal solutions which have a high viscosity: 0.1% solution in a 0.9% solution of NaCl at a temperature of 20° has a viscosity 12 times greater than that of water. Hyaluronidase is an enzyme which specifically depolymerizes and hydrolyzes hyaluronic acid. When hyaluronidase acts on the substrate there is during the first phase a destruction of the bond between the polysaccharide and protein portion of the hyaluronic acid which leads to the loss of its capacity for coagulating in an acid medium. According to MacClean this phase determines the increase in the permeability of membranes which include in their make-up a hyaluronic-protein complex. In the subsequent phase there is a depolymerization of the hyaluronic acid accompanied by a reduction in viscosity after which hydrolysis sets in with destruction of the glucoside bond between the glycuronic acid and the N-acetylglucosamine.

In determining the hyaluronidase activity one determines the highest dilution of the enzyme capable of inhibiting the formation of a mucin clot in the substrate following incubation at a temperature of 37° for 20 minutes in an acid medium.

Using this method we studied the hyaluronidase activity of the blood serum in 43 virtually healthy persons, in 65 with stomach cancer, 4 with cancer of the lungs, 5 with pulmonary abscess, 32 with gastric ulcer, 8 with intestinal cancer, 8 with gastritis, and 7 with benign tumors (lipomas, polyps, fibroma, leiomyoma).

The hyaluronidase activity of blood serum in virtually healthy persons varied from 0 to 2.5 h.u. (hyaluronidase units).

In stomach cancer patients in various stages the hyaluronidase activity of the blood serum fluctuated from 2.5 to 10 h.u. In 35 patients the hyaluronidase activity was between 5 and 10 h.u. and in the others it was 2.5 to 5 h.u. The high hyaluronidase activity of the blood serum in cancer patients has been indicated by N. A. Troitskaya, K. P. Balitskiy, F. A. Gluzman and others.

Of the 65 patients with stomach cancer 60 persons were operated on (1st, 2nd, 3rd and 4th stages of the disease). Radical surgery was performed on 31 patients (1st, 2nd and 3rd stages); in these patients the hyaluronidase activity varied between 5-6.7 hyaluronidase units, including a figure of 6.7 h.u. in 17 and 10 h.u. in 5 patients. Palliative resection was performed on 7 patients whose hyaluronidase activity was within 5 h.u. There were 22 nonoperable patients (3rd and 4th stages); here hyaluronidase activity was between 2.5 and 6.7 h.u.; in half of the patients it was 3.3 h.u. The reduction in the hyaluronidase activity in nonoperable patients can apparently be explained by the sharp disruption of the biochemical and metabolic processes in the body, the suppression of the entire enzyme system and pronounced cancerous intoxication.

F. A. Gluzman and K. P. Balitskiy have indicated that in cancer cases which have progressed rather far there is a marked change in liver function, including that of hyaluronidase formation, which possibly leads to the reduction in the hyaluronidase activity of the blood of such patients.

The hyaluronidase activity in patients given radical surgery (gastric resection) dropped from 6.7 to 2.5-3.3 h.u. by the time of discharge (10 days after surgery) while in those treated by laparotomy it did not change but remained at the former level -- 3.3-5 h.u.

In gastritis patients the hyaluronidase activity of the blood serum averaged 2.5 h.u. while in peptic ulcer of the stomach it was 3.3 h.u. Indolent ulcers which took a long time to heal in two cases gave a hyaluronidase activity of 6.7 h.u. (in one case malignization of the ulcer was determined pathohistologically).

Hyaluronidase activity in pulmonary cancer and abscess fluctuated in our patients from 3.3 to 5 h.u.

In intestinal cancer the hyaluronidase activity was from 2.5 to 3.3 h.u.

In the opinion of a number of authors (F. A. Gluzman, Pirie, Cowdry, Durand-Reynals, Stuart, etc.) hyaluronidase in tumors is one of the factors furthering metastasis and infiltrating growth by loosening the bonds between the individual tumor cells and increasing the permeability of the surrounding connective tissue.

It is characteristic that the blood serum of patients with benign tumors does not reveal any hyaluronidase activity.

Thus along with known data from the literature on the enzyme spreading factor (hyaluronidase) of substances of microbic and tissue (testicular) origin, we find the presence of a cancer hyaluronidase, occurring during the process of cancerogenesis, apparently commensurately with the disruption of metabolism. This corresponds to the view of A. A. Bogomolets as expressed by him as early as 1921, "The problem of enzymes of malignant tumors is still waiting solution. There is a doubtlessly correct view that tumor enzymes do not play a role in their destructive capacity. Here we must have mainly in mind the erosive action of the tumor enzymes on the surrounding tissues."

The diffusible factor (hyaluronidase), existing in the serum of cancer patients and in the tumors themselves, is an enzyme-protein complex, possessing biological properties as yet not greatly studied. This factor of an enzymatic nature is apparently a product of metabolic distortion, principally of protein metabolism, which is particularly disrupted in cancerogenesis.

Stomach cancer patients with a high hyaluronidase activity of the blood serum show, as a rule, an accelerated erythrocyte sedimentation rate and, on the other hand, the latter has produced low figures in patients with a low hyaluronidase activity, although the patients were in a severe, inoperable state; there was some positive correlation between the erythrocyte sedimentation rate and the hyaluronidase level in the blood of patients with stomach cancer.

In the patients under observation who had undergone stomach resection in the treatment of cancer, the hyaluronidase activity of the blood dropped as did the erythrocyte sedimentation rate.

The relation between erythrocyte sedimentation and the hyaluronic acid content of the blood has been indicated by S. M. Bychkov, S. Shidlovskiy, B. Zablotskiy and Z. Gorzelan.

#### CONCLUSIONS

1. The hyaluronidase activity of the blood during cancer increases to three- or fourfold that of the blood serum of healthy persons.

2. In stomach cancer of stages I, II or III the hyaluronidase activity of the blood serum was between 5-10 h.u., with an average of 6.3 h.u., while it was 4.2 h.u. in the fourth stage.

3. Ten days after radical surgery the hyaluronidase activity of the blood serum of patients dropped to 2.5-3.3 h.u. Palliative surgery did not produce any noticeable shifts in the hyaluronidase activity of the blood serum after 10 days.

4. There is some positive correlation between the erythrocyte sedimentation rate and the hyaluronidase activity of the blood serum in stomach cancer patients.

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